Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 17, 24, 25, 28-47 are pending in the application, with claim 17 being the independent claim. Claims 18-23 and 26-27 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein. New claims 35-47 are sought to be added. Support for amendments to claim 17 can be found in the specification, for example, at page 4, lines 15-19, and at page 4, line 25, through page 5, line 4. New claim 35 has been added to separate out an embodiment of previous claim 25. Support for new claims 36-42 can found in the specification, for example, at page 4, line 25, through page 5, line 4. Support for new claim 43 can be found in the specification, for example, at page 5, lines 1-4. Support for new claims 44-47 can found in the specification, for example, at page 5, line 27, through page 6, line 8. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Sequence Listing

In accordance with the Examiner's request, Applicants submit herewith another copy of the computer readable copy of the Sequence Listing, filed November 11, 2001. *See* Paper No. 11, page 2. In accordance with 37 C.F.R. § 1.821(f), the computer readable copy of the Sequence Listing submitted herewith is the same as the paper copy of the Sequence Listing

filed November 2, 2001. In accordance with 37 C.F.R. § 1.821(g), this submission includes no new matter.

Rejections Under 35 U.S.C. § 112, First Paragraph

Claim 32 was rejected under 35 U.S.C. § 112, first paragraph, allegedly for lack of enablement. *See* Paper No. 11, page 2.

As a threshold matter, the Examiner bears the initial burden of demonstrating a *prima facie* showing that the claims are not enabled. MPEP § 2164.04 reads, in pertinent part:

> In order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention. *Citing In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

S*ee also*, *In re Cortright*, 49 USPQ2d 1464, 1466 (Fed. Cir. 1999); *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971).

Claim 32 is drawn to a vaccine characterized in that the peptide is a tumor antigen. The Examiner relied on the abstract of Yamana H. and Itoh, K., "Specific immunotherapy with cancer vaccines," *Gan To Kagaku Ryoho* 27(10):1477-88 (2000), which states, in part:

> We have also established HLA-A24- and A26-restricted and cancer specific CTLs from a patient with squamous cell carcinoma of the esophagus. Using CTLs, we identified a new gene SART-1 by cDNA-expression cloning and some SART-1-derived cancer rejection peptides were also identified. Further more, using the same approach, we identified a cyclophilin B gene that encodes antigenic epitopes recognized by the HLA-A24-restricted and tumor specific CTLs. Now we are performing phase I trials using these peptide vaccines and have found an increase in CTL precursor frequency in some cases in an in vitro study.

> However, other recent studies have reported that many tumors escape from CTL recognition by downregulation of HLA class I expression. Moreover, most cancer cells produce a suppressor agents against the immune system. Therefore, we must resolve these major problems to produce successful cancer vaccine therapy soon.

The Examiner further relied on *In re Wright*, 999 F. 2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993), which stated that a vaccine "must by definition trigger and immunoprotective response in the host vaccinated; mere antigenic response is not enough." *See* Paper No. 11, page 3. The Examiner stated that in view of Yamana and Itoh, "successful cancer vaccine therapy still has to resolve major problems" and that "one of skill in the art would be forced into excessive experimentation to practice the broadly claimed invention in view of the lack of working examples, lack of guidance, and lack of success of others in the art." *Id.* Applicants respectfully traverse the rejections.

Most cancer vaccines are designed for *therapeutic* use. Applicants assert this important point because a medicine that is used therapeutically can be deemed effective and successful even if it does not cure disease. Applicants assert that, contrary to the sweeping, general statement in the abstract of Yamana and Itoh, cancer vaccine therapy has proven to be successful in clinical trials in the treatment of several cancers including, *inter alia,* melanoma[1] and lymphoma[2], both of which were shown prior to the publication date of Yamana and Itoh. It is asserted that the clinical efficacy of a cancer vaccine is based not

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[1]Rosenberg *et al.* "Impact of cytokine administration on the generation of antitumor reactivity in patients with metastatic melanoma receiving a peptide vaccine," *J. Immunol.* 163(3):1690-5 (1999). Exhibit A.

[2]Bendandi *et al.* "Complete molecular remission induced by patient-specific vaccination plus granulocyte-monocyte colony stimulating factor against lymphoma," *Nat. Med.* 5(10):1171-7 (1999). Exhibit B.

necessarily on complete cancer remission, but rather on, e.g., prolonged patient survival, i.e., the vaccine is therapeutic. Indeed, for treatment of advanced stage metastatic cancers, the most optimistic goals involve tumor regression which can prolong patient survival, and in fact such results have been obtained in melanoma vaccine trials. *See* Rosenberg *et al.*, fn. 1. Nonetheless, cancer vaccine therapy has shown remarkable success in the treatment of lymphoma, leading to complete remission in one study. *See* Bandandi *et al.*, fn. 2. Applicants assert that one of ordinary skill in the art would interpret these responses to the cancer vaccine as "immunoprotective responses" as set forth in *In re Wright*, 999 F. 2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Further, the Examiner has not provided any evidence or sound scientific reasoning why there is reason to doubt that one of ordinary skill in the art could, after reading the present specification, prepare *improved* vaccine compositions that have a greater efficacy towards tumor cells, even despite downregulation of HLA class I surface receptors. One aspect of the invention relates to vaccine formulations exhibiting enhanced immunogenicity of peptides derived from tumor antigens. Indeed, based on the disclosure of the captioned application, one of ordinary skill in the art would appreciate that an innovative way to counter the *decreased* expression of HLA class I expression in tumor cells would be to *increase* the activity of the CTLs to which the HLA receptors bind. In this way, the present invention solved the problem that Yamana and Itoh address.

Further, Applicants demonstrate in the Example in the captioned application that a significant percentage of mice injected with a vaccine of the invention remained tumor free after challenge with tumor cells relative to mice injected with a control vaccine. These results are *prima facie* evidence of enablement. Accordingly, Applicants respectfully

request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 112, first paragraph.

Rejections Under 35 U.S.C. § 112, Second Paragraph

Claim 17 and claims 18-34 dependent thereon were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for recitation of "low concentration of inorganic salts" because one of skill in the art would allegedly be unable to determine the metes and bounds of the claimed invention. Applicants respectfully traverse this rejection as it may be applied to the pending claims.

However, solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicants have amended claim 17 to recite "substantially free from inorganic salt ions." See below regarding "substantially free." Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claim 17 and claims 18-34 dependent thereon were rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for recitation of "highly purified" because one of skill in the art would allegedly be unable to determine the metes and bounds of the claimed invention. Applicants respectfully traverse this rejection as it may be applied to the pending claims.

However, solely to advance prosecution and not in acquiescence of the Examiner's rejection, Applicants have amended claim 17 to recite "purified." Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claims 18 and 19 were rejected under 35 U.S.C. § 112, second paragraph, as

allegedly being indefinite for recitation of "substantially free" because one of skill in the art would allegedly be unable to determine the metes and bounds of the claimed invention. Applicants have canceled claims 18 and 19 and have incorporated the term "substantially free" in amended independent claim 17. Applicants respectfully traverse this rejection as it may be applied to the pending claims.

Applicants assert that the specification provides guidance as to the meaning of the terms "substantially free":

> Preferably, the vaccine is substantially free from sodium, chloride and phosphate ions, and particularly preferably it is free from all inorganic salt ions ("substantially free" means that no salts have been added to the vaccine, but that there may be impurities present which have originated from reagents or there may be traces of ions; ions originating from adjuvants are not included in the calculation either, e.g. when using inorganic adjuvants).

Specification at page 3, line 27 through page 4, line 7. Thus, the claim is definite and Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claim 25 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for recitation of "slightly hypotonic" and that one of skill in the art would be unable to determine the metes and bounds of the claimed invention. Applicants respectfully traverse this rejection as it may be applied to the pending claims.

However, solely to advance prosecution and not in aquiescence of the Examiner's rejection, Applicants have deleted "slightly hypotonic" from claim 25. New claim 35 recites "hypotonic." Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection.

Claim 32 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly being

indefinite for recitation of "derived from" because it is allegedly unclear if the antigens are undergoing any kind of chemical modification as implied by the term "derived from." Applicants respectfully traverse this rejection.

Applicants assert that "derived from" is definite. Applicants direct the Examiner to the following excerpt of the specification:

> The antigens may be naturally occurring immunogenic proteins, e.g. proteins from viral or bacterial pathogens or the fragments thereof or cellular breakdown products in the form of peptides; or tumour antigens or fragments thereof. In a preferred embodiment the antigen is a tumour antigen or a natural or synthetic peptide derived therefrom; in this case the vaccine is a tumour vaccine.

Specification at page 6, lines 20-27. Applicants assert the above passage provides guidance as to the meaning of "derived from." For example, the antigens may be fragments and cellular breakdown products of antigenic proteins.

In view of the above, it is respectfully requested that the rejections under 35 U.S.C. § 112, second paragraph, be withdrawn.

Rejections Under 35 U.S.C. § 102

The Examiner rejected claims 17-32 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 5,776,468 (the '468 Patent). Applicants respectfully traverse the rejection as it may be applied to the pending claims.

The '468 Patent states "[t]he present invention provides a vaccine composition comprising an antigen in conjunction with 3-O-deacylated monophosphoryl lipid A (abbreviated herein to MPL) and a suitable carrier wherein the particle size of the MPL is

'small' and in general does not exceed 120 nm when prepared." *See* '468 Patent, at column 1, lines 37-42. Applicants further direct the Examiner's attention to the following excerpt of the '468 Patent, to support Applicants' assertion that the composition disclosed by the '468 Patent is not substantially free from inorganic salt ions as required by amended claim 17 of the captioned application:

> In order to maintain the MPL size in the 100 nm range after being formulated with aluminum hydroxide, the antigen and the buffer, Tween 80 (polyoxyethylene (20) sorbitan monooleate) or sorbitol can be added. Under these conditions, it has been established that MPL does not aggregate in the presence of phosphate buffer, *as may happen during formulation without them.* By doing so, the final formulation is further defined and characterized. (Emphasis added).

The '468 Patent at column 3, lines 46-54. Thus, the phosphate buffer is a component of the vaccine formulation in the '468 Patent; sorbitol or Tween 80 is added for the purpose of preventing aggregation of MPL particles induced by the presence of more than trace amounts phosphate ions in the vaccine composition.

In contrast, amended claim 17 requires that the vaccine be substantially free from inorganic salt ions. "'[S]ubstantially free' means that no salts have been added to the vaccine, but that there may be impurities present which have originated from reagents or there may be traces of ions; ions originating from adjuvants are not included in the calculation either, e.g. when using inorganic adjuvants." *Specification* at page 4, lines 1-6. The vaccine of claim 17 can contain only *trace* amounts of inorganic ions. Accordingly, Applicants submit that they have met their burden to distinguish the '468 Patent from Applicants' claims. The rejection under 35 U.S.C. §102(e) should be withdrawn.

Claims 17-34 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated

by Schmidt *et al.* (WO 97/30721). The Examiner alleged that the Schmidt *et al.* publication discloses pharmaceutical compositions containing a purified peptide and further containing an adjuvant, wherein the adjuvant is polyarginine. Applicants respectfully traverse the rejection as it may be applied to the pending claims.

Amended claim 17 requires that the vaccine contains one or more water soluble or emulsifiable substances which is capable of making the vaccine isotonic or hypotonic wherein the substance(s) is selected from the group consisting of: maltose, fructose, galactose, saccharose, sugar alcohol, lipid and combinations thereof. Applicants assert that Schmidt *et al.* does not disclose that these compounds can be used to make the vaccine composition isotonic or hypotonic. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §102(b).

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

In the claims:

Claims 18-23 and 26-27 were canceled.

The following claims were amended:

17. (once amended) Vaccine containing one or more synthetic or [highly] purified natural peptides or proteins as antigen(s) as well as one or more adjuvants, characterised in that it is present as a solution or emulsion which is substantially free from inorganic salt ions, [or has a low concentration of inorganic ions] wherein said solution or emulsion contains one or more water soluble or water-emulsifiable substances which is capable of making the vaccine isotonic or hypotonic, said substance(s) selected from the group consisting of:

a) a maltose;

b) a fructose;

c) a galactose;

d) a saccharose;

e) a sugar alcohol;

g) a lipid; and

h) combinations thereof.

24. (once amended) Vaccine according to claim [23] 36, characterized in that the sugar alcohol is sorbitol.

25. (once amended) Vaccine according to claim [20] 17, characterized in that said water soluble or water-emulsifiable [the isotonic-making] substance is present in a concentration such that the resulting solution is isotonic [or slightly hypotonic].

28. (once amended) Vaccine according to claim [17] 36, characterized in that the concentration of sugar alcohol is in the range from about 200-400 mM.

New claims 35-47 were added.